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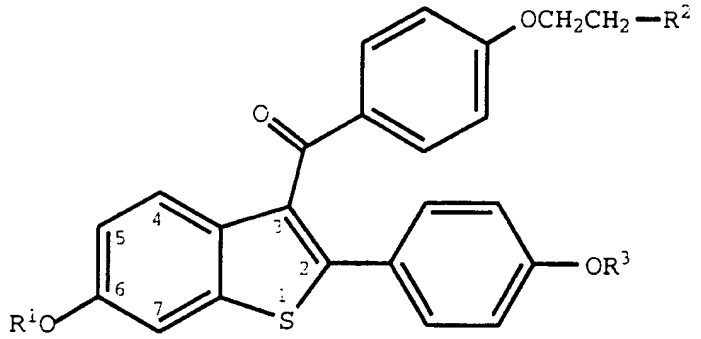
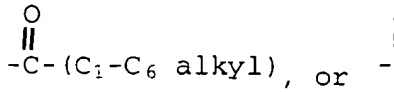
(54) 2-Phenyl-3-azoylbenzothiophenes for treating obsessive-compulsive and consumptive disorders.

(57) A method of inhibiting obsessive-compulsive or consumptive disorders comprising administering to a human in need thereof an effective amount of a compound having the formula



(I)

wherein R^1 and R^3 are independently hydrogen, $-CH_3$,



wherein Ar is optionally substituted ph nyl ;

R^2 is select d from th group consisting of pyrrolidine, hexam thyl neamino, and piperidino ; or a pharmaceutically acceptabl salt of solvat thereof.

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Obsessive-compulsive disord r is one of th rarer psychiatric illn sses, although minor obs ssional symptoms probably occur in one-sixth of the population (*Encyclopedia of M dicin* , American Medical Association; *Current Diagnosis,* W.B.Saunders Company, 1985). It is characteriz d by one or both of two symptoms. Th first comprises r curr nt, intrusive ruminativ thoughts that the patient may realiz are sensel ss but of which he cannot stop thinking. The most common of these are thoughts of violence, contamination, doubt, or personal illness. Normally, the patient does not believe these thoughts are true reflections of reality. However, some patients become convinced that their obsessive ruminations are true, and suffer from psychotic delusions.

The second comprises repetitive, ritualistic behaviors that the patient recognizes are needless but that he cannot keep himself from performing. Hand washing, counting, checking rituals, and touching rituals are examples of such rituals. The carrying out of the ritual is not constant, but fluctuates and mirrors anxiety levels. There normally are intense feelings of panic and anxiety if the patient is prevented from completing a ritual.

While appearing depressed a review of the history of obsessive-compulsive patients normally reveals that obsessions and compulsions precede the onset of dysphoric mood states and that depressed feelings are related to the impact the obsessive-compulsive behaviour has on life. In severe cases, the patient will be incapacitated, completely overtaken by the distraction of constant obsessive ruminations or the demand to complete endless compulsive rituals.

Consumptive disorders include those disorders in which the intake, normally oral, of the amount of a substance is outside a normal range, often to an extent where health is impaired. Examples of such are eating or appetite disorders (obesity, bulimia, pica, anorexia nervosa, and psychogenic rumination) and substance abuse or overuse (smoking, nicotine dependence, alcoholism, alcohol abuse).

It is well known that the chronic administration of nicotine results in tolerance and, eventually, dependence. The use of tobacco has become extremely widespread in all countries, despite the well known adverse effects of the use of tobacco in all its forms. Thus, it is clear that tobacco use is extremely habit-forming, if not addictive, and that its use provides sensations to the user which are pleasant and welcome, even though the user is fully aware of the drastic long term ill effects of its use.

Cigarette smoking is the most dominant cause of preventable morbidity and early demise in developed countries. On average, smokers die several years earlier than nonsmokers and have an increased risk of fatal heart disease, lung cancer, cancers of the mouth, throat, esophagus, pancreas, kidney, bladder, and cervix, peptic ulcers and of fractures of the hip, wrist, and vertebrae. Olfaction and taste are impaired in smokers, and facial wrinkles are increased. Diabetic patients who smoke may have an increased risk of proteinuria.

Smoking cessation provides benefits, even late in life, such as reducing the risk of death or myocardial infarction in persons with coronary artery disease, reducing the progression of carotid atherosclerosis, and with reversal of chronic bronchitis.

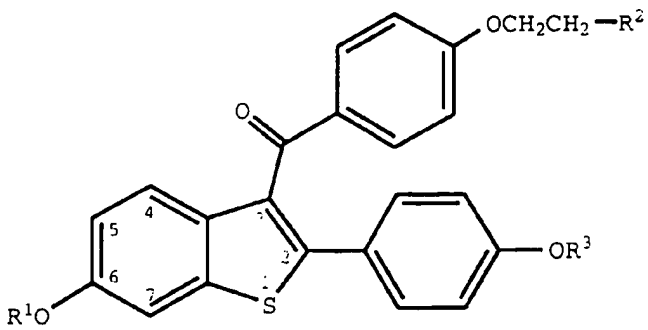
Children of persons who smoke have lower birth weights, more frequent respiratory infections, less efficient pulmonary function, and a higher incidence of chronic ear infections than children of non-smokers and are more likely to become smokers themselves. Exposure to passive smoke has been shown to increase the risk of cervical cancer, lung cancer, and heart disease and to promote endothelial damage and platelet aggregation.

Recently, vigorous campaigns against the use of tobacco have taken place, and it is now common knowledge that the cessation of smoking brings with it numerous unpleasant withdrawal symptoms, which include irritability, anxiety, restlessness, lack of concentration, lightheadedness, insomnia, tremor, increased hunger and weight gain, and, of course, a craving for tobacco.

Alcohol abuse and alcohol dependence (i.e., alcoholism) are serious public health problems of modern society. In the United States alone, an estimated 13 million adults exhibit symptoms of alcohol dependence due to excessive alcohol intake, and an additional 7 million abuse alcohol without showing symptoms of dependence according to U.S. government projections from studies conducted in the mid-1980s. Alcohol dependence and abuse are very expensive as it is estimated that it cost the U.S. well over $200 billion in 1991 with no prospect of falling or leveling off. The social and psychological damages inflicted on individuals as a consequence of alcohol abuse, e.g., children born with fetal alcohol syndrome (FAS) and victims of alcohol-related accidental death, homicide, suicide, etc., are immense.

While it is generally accepted that alcoholism and alcohol abuse are affiliations with staggering international economic, social, medical, and psychological repercussions, success in preventing or otherwise ameliorating the consequences of these problems has been an elusive goal. Only very recently the public view that alcoholism and alcohol abuse are remediable solely by moral imperatives has been changed to includ an awar ness of alcoholism and alcohol abuse as physiological ab rrations whos tiology may be understood and for which therapy may be found through sci ntific pursuits. Both alcohol abuse and dep ndence aris as a result of different, complex, and as yet incompletely understood process s. At pr sent, alcohol research is in the mainstream of sci ntific fforts.

This invention provides methods for inhibiting obsessive-compulsive or consumptive disorders comprising administering to a human in need thereof an effective amount of a compound of formula I



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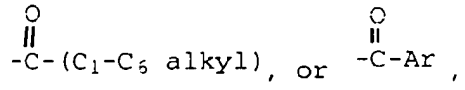


wherein Ar is optionally substituted phenyl;

R^2 is selected from the group consisting of pyrrolidino, hexamethyleneimino, and piperidino; and pharmaceutically acceptable salts and solvates thereof.

The current invention concerns the discovery that a select group of 2-phenyl-3-aroylbenzothiophenes (benzothiophenes), those of formula I, are useful for inhibiting obsessive-compulsive and consumptive disorders and their symptoms. The therapeutic and prophylactic treatments provided by this invention are practiced by administering to a human in need thereof a dose of a compound of formula I or a pharmaceutically acceptable salt or solvate thereof, that is effective to inhibit obsessive-compulsive or consumptive disorders or their symptoms. The term inhibit is defined to include its generally accepted meaning which includes prophylactical administration to a human subject to incurring the disorders or symptoms described, and holding in check and/or treating an existing disorder or symptom. As such, the present method includes both medical therapeutic and/or prophylactic administration, as appropriate.

Raloxifene is a preferred compound of this invention and it is the hydrochloride salt of a compound of formula 1 wherein R^1 and R^3 are hydrogen and R^2 is 1-piperidinyl.

The invention encompasses methods for the treatment of alcoholism or alcohol abuse, for alcohol sensitization, for extinguishing an alcohol-drinking response, for suppressing an urge for alcohol, for inducing alcohol intolerance, and for preventing alcoholism in an individual with or without susceptibility to alcoholism or alcohol abuse, or for limiting alcohol consumption in an individual whether or not genetically predisposed.

The method of the present invention also encompasses assisting persons who want to cease or reduce their use of tobacco or nicotine. Most commonly, the form of tobacco use is smoking, most commonly the smoking of cigarettes. The present invention is also helpful, however, in assisting in breaking the habit of all types of tobacco smoking, as well as the use of snuff, chewing tobacco, etc. The present method is also helpful to those who have replaced, or partially replaced, their use of tobacco with the use of nicotine replacement therapy. Thus, such patients can be assisted to reduce and even eliminate entirely their dependence on nicotine in all forms.

Generally, at least one compound of formula I is formulated with common excipients, diluents or carriers, and compressed into tablets, or formulated as elixirs or solutions for convenient oral administration, or administered by the intramuscular or intravenous routes. The compounds can be administered transdermally, and may be formulated as sustained release dosage forms and the like.

The compounds used in the methods of the current invention can be made according to stablished procedures, such as those detailed in U.S. Patent Nos. 4,133,814, 4,418,068, and 4,380,635 all of which are incorporated by reference herein. In general, the process starts with a benzo[b]thiophen having a 6-hydroxyl

group and a 2-(4-hydroxyph nyl) group. Th starting compound is protected, acylat d, and deprotected to form th formula I compounds. Exampl s of the preparation of such comp unds are provided in the U.S. patents discuss d abov . The term "optionally substituted phenyl" includes ph nyl and phenyl substituted onc or twic with C_1-C_6 alkyl, C_1-C_4 alkoxy, hydroxy, nitro, chloro, fluoro, or tri(chloro or fluoro)m thyl.

The compounds us d in the methods of this inv ntion form pharmaceutically acc ptable acid and base addition salts with a wide variety of organic and inorganic acids and bases and include the physiologically acceptable salts which are often used in pharmaceutical chemistry. Such salts are also part of this invention. Typical inorganic acids used to form such salts include hydrochloric, hydrobromic, hydroiodic, nitric, sulfuric, phosphoric, hypophosphoric and the like. Salts derived from organic acids, such as aliphatic mono and dicarboxylic acids, phenyl substituted alkanoic acids, hydroxyalkanoic and hydroxyalkandioic acids. aromatic acids, aliphatic and aromatic sulfonic acids, may also be used. Such pharmaceutically acceptable salts thus include acetate, phenylacetate, trifluoroacetate, acrylate, ascorbate, benzoate, chlorobenzoate, dinitrobenzoate, hydroxybenzoate, methoxybenzoate, methylbenzoate, o-acetoxybenzoate, naphthalene-2-benzoate, bromide, isobutyrate, phenylbutyrate, β-hydroxybutyrate, butyne-1,4-dioate, hexyne-1,4-dioate, caprate, caprylate, chloride, cinnamate, citrate, formate, fumarate, glycollate, heptanoate, hippurate, lactate, malate, maleate, hydroxymaleate, malonate, mandelate, mesylate, nicotinate, isonicotinate, nitrate, oxalate, phthalate, teraphthalate, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, propiolate, propionate, phenylpropionate, salicylate, sebacate, succinate, suberate, sulfate, bisulfate, pyrosulfate, sulfite, bisulfite, sulfonate, benzene-sulfonate, p-bromophenylsulfonate, chlorobenzenesulfonate, ethanesulfonate, 2-hydroxyethanesulfonate, methanesulfonate, naphthalene-1-sulfonate, naphthalene-2-sulfonate, p-toluenesulfonate, xylenesulfonate, tartarate, and the like. A preferred salt is the hydrochloride salt.

The pharmaceutically acceptable acid addition salts are typically formed by reacting a compound of formula I with an equimolar or excess amount of acid. The reactants are generally combined in a mutual solvent such as diethyl ether or benzene. The salt normally precipitates out of solution within about one hour to 10 days and can be isolated by filtration or the solvent can be stripped off by conventional means.

Bases commonly used for formation of salts include ammonium hydroxide and alkali and alkaline earth metal hydroxides, carbonates, as well as aliphatic and primary, secondary and tertiary amines, aliphatic diamines. Bases especially useful in the preparation of addition salts include ammonium hydroxide, potassium carbonate, methylamine, diethylamine, ethylene diamine and cyclohexylamine.

The pharmaceutically acceptable salts generally have enhanced solubility characteristics compared to the compound from which they are derived, and thus are often more amenable to formulation as liquids or emulsions.

Pharmaceutical formulations can be prepared by procedures known in the art. For example, the compounds can be formulated with common excipients, diluents, or carriers, and formed into tablets, capsules, suspensions, powders, and the like. Examples of excipients, diluents, and carriers that are suitable for such formulations include the following: fillers and extenders such as starch, sugars, mannitol, and silicic derivatives; binding agents such as carboxymethyl cellulose and other cellulose derivatives, alginates, gelatin, and polyvinyl pyrrolidone; moisturizing agents such as glycerol; disintegrating agents such as calcium carbonate and sodium bicarbonate; agents for retarding dissolution such as paraffin; resorption accelerators such as quaternary ammonium compounds; surface active agents such as cetyl alcohol, glycerol monostearate; adsorptive carriers such as kaolin and bentonite; and lubricants such as talc, calcium and magnesium stearate, and solid polyethyl glycols.

The compounds can also be formulated as elixirs or solutions for convenient oral administration or as solutions appropriate for parenteral administration, for instance by intramuscular, subcutaneous or intravenous routes. Additionally, the compounds are well suited to formulation as sustained release dosage forms and the like. The formulations can be so constituted that they release the active ingredient only or preferably in a particular part of the intestinal tract, possibly over a period of time. The coatings, envelopes, and protective matrices may be made, for example, from polymeric substances or waxes.

The particular dosage of a compound of formula I required to inhibit obsessive-compulsive or consumptive disorders or their symptoms, according to this invention, will depend upon the severity of the condition, the route of administration, and related factors that will be decided by the attending physician. Generally, accepted and effective daily doses will be from about 0.1 to about 1000 mg/day, and more typically from about 50 to about 200 mg/day. Such dosages will be administered to a subject in need thereof from once to about three times each day, or mor often as n ded to effectively tr at or prevent the disord r(s) or symptom(s).

It is usually preferred to administer a compound of formula I in th form of an acid addition salt, as is customary in the administration of pharmaceuticals bearing a basic group, such as the piperidino ring. It is pr - f rred to administer a compound of the invention to an aging human (.g. a post-menopausal f male). For such purpos s the following oral dosage forms are availabl .

Formulations

In the formulations which follow, "Active ingr dient" means a compound of formula I.

Formulation 1: Gelatin Capsules

Hard gelatin capsules are prepared using the following:

Ingredient	Quantity (mg/capsule)
Active ingredient	0.1 - 1000
Starch, NF	0 - 650
Starch flowable powder	0 - 650
Silicon fluid 350 centistokes	0 - 15

The ingredients are blended, passed through a No. 45 mesh U.S. sieve, and filled into hard gelatin capsules.
Examples of specific capsule formulations of raloxifene that have been made include those shown below:

Formulation 2: Raloxifene capsule

Ingredient	Quantity (mg/capsule)
Raloxifene	1
Starch, NF	112
Starch flowable powder	225.3
Silicone fluid 350 centistokes	1.7

Formulation 3: Raloxifene capsule

Ingredient	Quantity (mg/capsule)
Raloxifene	5
Starch, NF	108
Starch flowable powder	225.3
Silicone fluid 350 centistokes	1.7

Formulation 4: Raloxifene capsule

Ingredient	Quantity (mg/capsule)
Raloxifene	10
Starch, NF	103
Starch flowable powder	225.3
Silicone fluid 350 c ntistok s	1.7

Formulation 5: Raloxif ne capsul

Ingredient	Quantity (mg/capsule)
Raloxifene	50
Starch, NF	150
Starch flowable powder	397
Silicone fluid 350 centistokes	3.0

The specific formulations above may be changed in compliance with the reasonable variations provided.
A tablet formulation is prepared using the ingredients below:

Formulation 6: Tablets

Ingredient	Quantity (mg/tablet)
Active ingredient	0.1 - 1000
Cellulose, microcrystalline	0 - 650
Silicon dioxide, fumed	0 - 650
Stearate acid	0 - 15

The components are blended and compressed to form tablets.

Alternatively, tablets each containing 0.1 - 1000 mg of Active ingredient are made up as follows:

Formulation 7: Tablets

Ingredient	Quantity (mg/tablet)
Active ingredient	0.1 - 1000
Starch	45
Cellulose, microcrystalline	35
Polyvinylpyrrolidone (as 10% solution in water)	4
Sodium carboxymethyl cellulose	4.5
Magnesium stearate	0.5
Talc	1

The Active ingredient, starch, and cellulose are passed through a No. 45 mesh U.S. sieve and mixed thoroughly. The solution of polyvinylpyrrolidone is mixed with the resultant powders which are then passed through a No. 14 mesh U.S. sieve. The granules so produced are dried at 50°-60° C and passed through a No. 18 mesh U.S. sieve. The sodium carboxymethyl starch, magnesium stearate, and talc, previously passed through a No. 60 U.S. sieve, are then added to the granules which, after mixing, are compressed on a tablet machine to yield tablets.

Suspensions each containing 0.1 - 1000 mg of Active ingredient per 5 mL dose are made as follows:

Formulation 8: Susp nsions

Ingredient	Quantity (mg/5 ml)
Active ingredient	0.1 - 1000 mg
Sodium carboxymethyl cellulose	50 mg
Syrup	1.25 mg
Benzoic acid solution	0.10 mL
Flavor	q.v.
Color	q.v.
Purified water to	5 mL

The Active ingredient is passed through a No. 45 mesh U.S. sieve and mixed with the sodium carboxymethyl cellulose and syrup to form a smooth paste. The benzoic acid solution, flavor, and color are diluted with some of the water and added, with stirring. Sufficient water is then added to produce the required volume.

ASSAYS

Assay 1

In order to demonstrate the *in vivo* effect of the compounds on alcohol consumption, experiments are designed to test the effect on free choice ethanol intake in golden hamsters. Hamsters are chosen based on previous reports that they are receptive to and give preference to high ethanol intake when compared with several other mammalian species. Kulkosky and Cornell (Pharmacol. Biochem. & Behav. 11:439-44, 1979) concluded that the species differences in ethanol intake and preferences were correlated with differences in ethanol metabolism.

The animals used for the experiments described herein are two to six male adult golden hamsters. Animals are maintained on a light/dark cycle of 14 hours of light per day and for a 6-week acclimation period. Animals have access to food and water *ad libitum*.

For the experiment, the animals are maintained as described above in a single large cage with four 250 ml calibrated drinking bottles. The drinking bottles are fitted with stainless steel straight sipper tubes used to measure fluid consumption to the nearest 5 ml. Spillage from the drinking tubes is caught by 2 oz. jars fitted with glass funnels and positioned under the sipper tubes. Fluid consumption by the hamsters is measured once every 3 days so that the consumption volumes are large enough to obtain reasonably accurate measurements.

After a 6-week acclimation period, the body weights of the animals are taken, and water intake is noted. Water in 2 of the 4 drinking bottles is then replaced by a 15% ethanol solution and consumption of water and aqueous ethanol are measured for a period of 2 weeks. Within 2 to 3 days after the beginning of this free choice phase of feeding, the hamsters establish an explicit preference for aqueous ethanol over water and the initial preference ratio (aqueous ethanol intake divided by water intake) is noted.

As a control, the animals are then fed with 0.2 ml water twice daily, using a stainless steel animal feeding needle. Water feeding does not seem to have any effect on the animals' drinking behavior as measured by total fluid intake. After 6 days, the same group of hamsters are fed a compound of formula I via a liquid mixture for a period of 3 to 12 weeks. Activity of the compounds of formula I is illustrated by the preference ratio being lower during administration of said compound of the invention than the initial preference ratio.

ASSAY 2

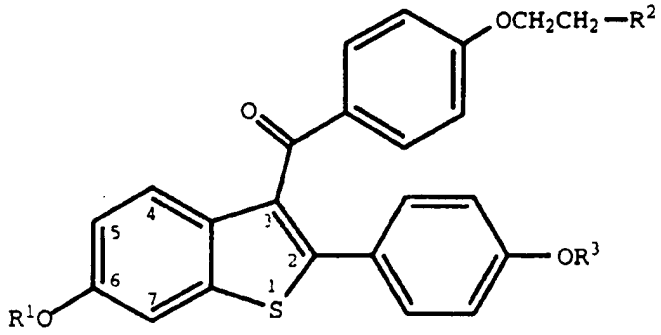
Five to fifty women are selected for the clinical study. The women are post-menopausal, i.e., have ceased menstruating for between 6 and 12 months prior to the study's initiation, are in good general health, and suffer from ither obsessive-compulsiv or a consumptive disorder. Because of the idiosyncratic and subjectiv natur of these disorders, th study has a placebo control group, i.e., the women are divided into two groups, one of which receiv s raloxifen as th activ agent and the other receives a placebo. Women in the test group receive between 50-200 mg of th drug per day by the oral route. They continue this therapy for 3-12 months.

Accurate records are kept as t th number and severity of the symptoms in both groups and at th end of the study these results are compared. Th results are compared both b tween memb rs of ach group and also the results for each patient ar compared to th symptoms reported by each patient before the study began.

Utility of th compounds of formula I is illustrated by the positiv impact they have on one or more of the disorders/symptoms when used in an assay described above.

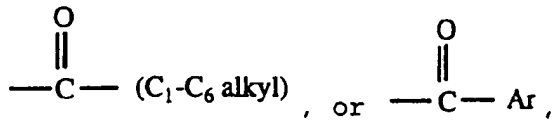
Claims

1. The use of a compound having the formula



(I)

wherein R^1 and R^3 are independently hydrogen, $-CH_3$,



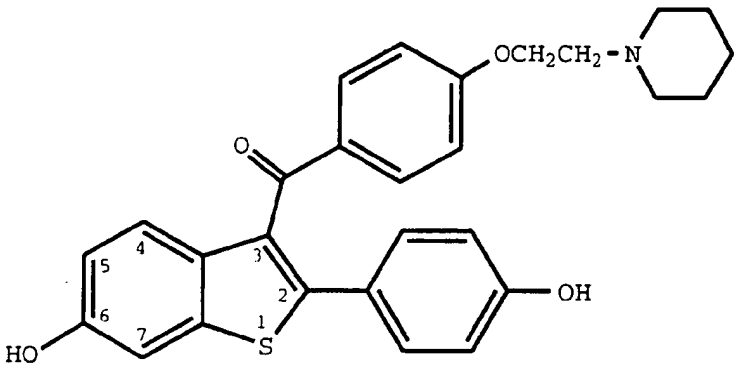
wherein Ar is optionally substituted phenyl;

R^2 is selected from the group consisting of pyrrolidino and piperidino; or a pharmaceutically acceptable salt or solvate thereof, in the preparation of a medicament useful for inhibiting obsessive compulsive disorder.

2. The use of Claim 1 wherein said compound is the hydrochloride salt thereof.

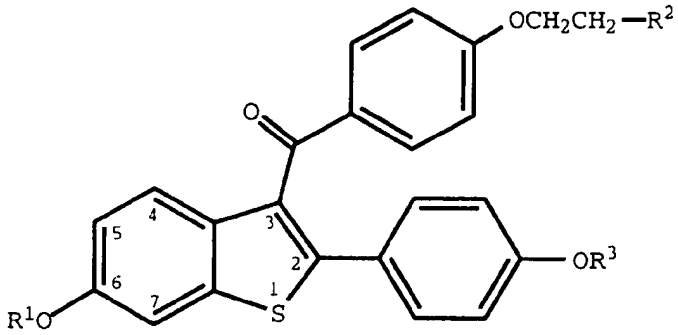
3. The use of Claim 1 wherein said medicament is prophylactic.

4. The use of Claim 1 wherein said compound is



or its hydrochloride salt.

5. The use of a compound having the formula



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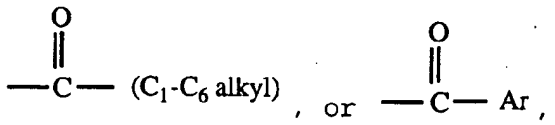


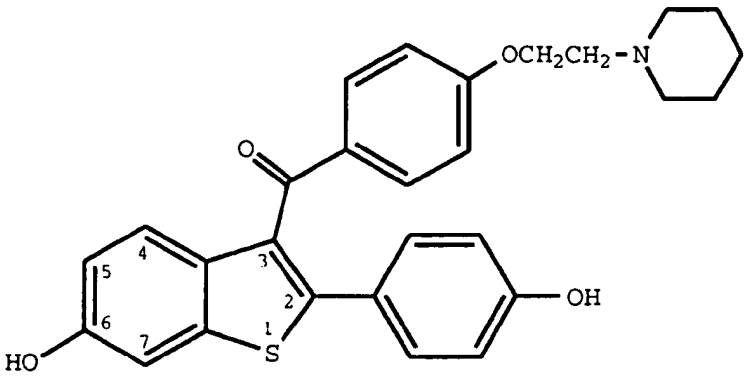
wherein Ar is optionally substituted phenyl;

R^2 is selected from the group consisting of pyrrolidino and piperidino; or a pharmaceutically acceptable salt or solvate thereof, in the preparation of a medicament useful for inhibiting a consumptive disorder.

6. The use of Claim 5 wherein said compound is the hydrochloride salt thereof.

7. The use of Claim 5 wherein said medicament is prophylactic.

8. The use of Claim 5 wherein said compound is



or its hydrochloride salt.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number
EP 94 30 9486

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
A	THE AMERICAN JOURNAL OF PSYCHIATRY, vol. 150, no.7, July 1993 pages 1131-1132, D.J. STEIN ET AL. 'PREGNANCY AND OBSESSIVE-COMPULSIVE DISORDER' * the whole document * ---	1-4	A61K31/445 A61K31/40 A61K31/38
A	JOURNAL OF THE AMERICAN DIETETIC ASSOCIATION, vol. 89, no.11, 1989 pages 1640-1646, L.G. TOLSTOI ET AL. 'THE ROLE OF PHARMACOTHERAPY IN ANOREXIA NERVOSA AND BULIMIA' * abstract; table 1 * ---	5-8	
D,A	US-A-4 133 814 (JONES ET AL.) 9 January 1979 * abstract; claims * ---	1-8	
D,A	US-A-4 418 068 (JONES) 29 November 1983 * abstract; claims * ---	1-8	TECHNICAL FIELDS SEARCHED (Int.Cl.6) A61K
A	JOURNAL OF MEDICINAL CHEMISTRY, vol. 27, no.8, 1984 pages 1057-1066, C.D. JONES ET AL. 'ANTIESTROGENS.2.' * the whole document * -----	1-8	

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	23 March 1995	Hoff, P

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
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T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

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